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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/076,074 | 02/15/2002 | Matthew C. Coffey | 032775-091 | 8498 |

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| EXAMINER | |
|---|---|
| LI, BAO Q | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/076,074 | COFFEY ET AL. | |
| | Examiner | Art Unit | |
| | Bao Qun Li | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1030* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/30/03& 05/14/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of Group I, claim 1-11 are in Paper No. 10 is acknowledged. The traversal is on the ground(s) that there are not serious burdens for searching groups I to III together. Applicants' argument has been fully considered. Groups I to II are rejoined.

2. Since applicants do not point out any error about the restricted group IV, the rest of restriction requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-30are considered before the examiner.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1, 12, and 26 are indefinite in that the recitations of "effective amount" of reovirus and chemotherapeutic agent are not defined either by the claim or specification. It is not clear what the function the amount is required to effect. Is the intent an effective amount of a reovirus and an effective amount of chemotherapeutic agent to sensitize the neoplastic cell or to kill the neoplastic cell? This affects the dependent claims 2-11, 13-25 and 27-30.

### *Claim Rejections - 35 USC § 112*

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-6, 8-11, 12-25, 26-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having a method for increasing the sensitivity of a ras-transformed C3H cells to cisplatin, a chemotherapeutic agent by using a reovirus, does not reasonably provide enablement for having a method for sensitizing any or all neoplastic cell to any or all therapeutic agent by reovirus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

10. 1) & 2) State of art and unpredictability. The use of reovirus to oncolyze the ras-mediated neoplasm is known in the art because the activated ras oncogene can inhibit the host cell PKR-interferon induction pathway and let the reovirus to replicate in the oncogenic ras expressed neoplastic cells; resulting in the neoplastic cells undergo apoptosis. This process is called oncolysis and the reovirus is categorized as an oncolytic virus (See Coffey, M.C. et al. Science 1998, Vol. 282, pp. 1332-1334, entire document). However, the art does not teach that any or all neoplastic cells, especially the neoplastic cells without oncogenic ras expression would be also sensitive to the oncolytic virus (see Strong, J.E. et al. EMBO J. 1998, Vol. 17, pp. 3351-3362, especially Fig. 9 on pp. 3359).

11. State of art also teaches that cancer cells frequently developed an almost uncanny ability to resist the effects of anticancer drugs. There are many mechanisms for anti-cancer therapy drugs and there are many mechanisms for cancer cells to develop the drug resistance (See website www.acs.ohio-state.edu/units/cancer/handbook/resist.pdf). For example, cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers, it has encountered the drug resistance operated by a number of mechanisms postulated by Furtes et al. (Current medicine Chemistry 2003, Vol. 10, 257-266, see entire document, especially Fig. 1

on page 258, Fig. 3 on page 262, and Fig. 4 on page 263). However, none of which is fully understood.

12. Taxol is a "billion dollar molecule" used for treatment of cancer through another mechanism and it also develops a drug resistance after treatment. Both the anti-cancer mechanism and drug resistance are different from cisplatin. (See Orr et al. Oncogen 20003, Vol. 22, pp. 7280-7295). The mechanism of using interferon for treating cancer patient also has complete different mechanism than most chemically synthesized compound drugs, which is through up-regulate the patient immune system and enhance the cellular immune response of T cell and NK cell activities (See Chaper II, page 331-334 in Textbook of Immunology, edited by Bona et al. 1996, Hardwood Academic Publishers).

13. Therefore, it is unpredictable that any or all drug resistance can be overcome or the sensitivity of the neoplastic cell can be increase by reovirus.

14. 3) & 4) Number of working examples and amount of guidance. Specification only teaches that pre-treatment of mice having a ras-mediated tumors with 5-$10^8$ PFUs of reovirus increase the sensitivity of the tumor cell to the cisplatin (2.5 mk/kg). However, the specification does not teach the sensitivities of any or all neoplastic cells to any other therapeutic agents as cited in claim 6 are increased by the treatment of reovirus. Because the specification does not teach all the chemotherapeutic agents exhibit the anti-cancer activities through a same mechanism, and the drug resistances for all cited drugs develop through the same mechanism. It is unpredictable that sensitivity of any kind of neoplastic cells to the chemotherapeutic agent will be increase by the treatment of reovirus. The specification lacks of teaching what the second chemotherapeutic agent is.

15. 5) Scope of the claims. The claims broadly read on a method of sensitizing any or all neoplastic cells by reovirus treatment and to a second any or all chemotherapeutic agent different fro the one that they are tested.

16. 6) Nature of the invention. The invention involves one of the most complex and unpredictable fields of cancer therapy and drug resistance.

17. 7) Lever of the skill in the art. The level of the skill in the cancer therapy is high.

18. Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan

would have to conduct undue and excessive experimentation in order to practice the claimed invention.

19. Claims 1-5, 8-11, 12-25, 26-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. In the instant case, while applicants have shown that they have a method of using reovirus increase the sensitivity of a ras-mediated tumor to cisplatin, it does no show that the Applicants as the invention was filed has the possession of a method to increase the sensitivity of any or all neoplastic cell to any or all chemotherapeutic drugs or to a second chemotherapeutic agent. The specification lacks of teaching what the second chemotherapeutic agent is.

21. Applicants are reminded that 35 USC 112 requires inter alia that "a patent specification contain a written description of the invention and the manner and process of making and using it in such full clear and concise terms as to enable one skilled in the art to make and use the invention". In the instant case, while dosage of the chemotherapeutic drug and reovirus are known in the art; the "written description" and an "enabling disclosure" are separate issue. For example, where a specification contains sufficient information to enable a skilled chemist to produce a particular compound because it gives detailed information on how to produce analogous compounds but it makes no reference to the compound in question, the "written description" requirement has not been met even though the description may be enabling.

***Double Patenting***

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

23. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

24. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claims 1-5, 8-11, 12-25, 26-28 and 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-22 of copending Application No. 10,602,024. Although the conflicting claims are not identical, they are not patentably distinct from each other because scopes of conflict claims all read on a method of reducing a neoplasm growth in an animal by using a reovirus and a chemotherapeutic agent together consequentially or concurrently. Because the Ras-activated neoplasm is a very common neoplasm among tumors or cancers, this species of the tumor as claimed in the application No. 10,602,024 includes and anticipates the general claimed any or all neoplasm in the current application. Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 1-6, 8-11, 12-13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 11-18, 22, 23, 25, 26, 27, 28, 32, 33-34 of U.S. Patent No. 6,565,831B1. Although the conflicting claims are not identical, they are not patentably distinct from each other, the scopes of conflict claims all overlapping and anticipated each other because they both

broadly read on a method of reducing a neoplasm growth in an animal by using a reovirus and a chemotherapeutic agent together consequentially or concurrently. Since Ras-activated neoplasm is a very common neoplasm among tumors or cancers, this species of the tumor as claimed in U.S. Patent No. 6,565,831B1 includes and anticipates the general claimed any or all neoplasm in the current application.

27. Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo. Therefore the scopes of conflict claims are overlapping.

28. Claims 1-6, 8-11, 12-13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-8,13-20, 24-33 and 34 of U.S. Patent No. 6,136,307A. Although the conflicting claims are not identical, they are not patentably distinct from each other, the scopes of conflict claims all overlapping and anticipated each other because they both broadly read on a method of reducing a neoplasm growth in an animal by using a reovirus and a chemotherapeutic agent together consequentially or concurrently. Since Ras-activated neoplasm is a very common neoplasm among tumors or cancers, this species of the tumor as claimed in U.S. Patent No. 6,565,831B1 includes and anticipates the general claimed any or all neoplasm in the current application.

29. Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo. Therefore the scopes of conflict claims are overlapping.

***Claim Rejections - 35 USC § 102***

30. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

31. Claims 1, 2, 3, 4, 5, 6, 8, 9, 12-14, 17-23, 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Robert et al. (WO 99,18799A1).

32. Robert et al. teach a method of treating neoplasm in a mammal comprising administration of reovirus and INF into a mammal suffering a neoplasm (See claims 1-3, 6-8, 22, 55 and 56). Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo. Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo. Therefore, the claimed invention is inherently anticipated by the cited reference.

33. Claims 1, 4, 8, 12, 17, 19, 20, 22, 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Mercer University (Mercer University Home page 1996, pp. 1-2) .

34. Mercer University published on its home page that disclose that Dr. Steele give mice a combination of reovirus type 3 and a chemotherapeutic compound BCUN , resulting in 100% implanted tumor reduction (see entire document). Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of

neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo. Therefore, the claimed invention is inherently anticipated by the cited reference.

35. Claims 1, 4, 8, 12, 17, 19, 20, 22, 26 are rejected under 35 U.S.C. 102(b) as being anticipated by William et al. (Cancer Immunol. Tmmunother. 1986, Vol. 23 (2), pp. 87-92).

36. William teach a method of treating neoplastic cells with a chemotherapeutic compound BCNU and reovirus in vitro and inhibit the tumor cell proliferation and growth (See entire document). Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro. Therefore, the claimed invention is inherently anticipated by the cited reference.

***Claim Rejections - 35 USC § 102***

37. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

38. Claims 1, 2, 3, 4, 5, 6, 8, 9, 12-14, 17-23, 26-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Lee et al. (US Patent No. 6,136,307A).

39. Lee et al. teach a method of treating ras-mediated proliferation disorder in a mammal comprising administration of a reovirus or a pharmaceutical composition comprising a reovirus and a chemotherapeutic agent into a mammal suffering a neoplasm (See lines 11-14 on col. 11 and claims 1, 3-8,13-20, 24-33 and 34). Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo.

Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo. Therefore, the claimed invention is inherently anticipated by the cited reference.

40. Claims 1, 2, 3, 4, 5, 6, 8, 9, 12-14, 17-23, 26-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Lee et al. (WO 00/50051A2).

41. Lee et al. teach a method of treating ras-mediated proliferation disorder in a mammal comprising administration of a reovirus or a pharmaceutical composition comprising a reovirus and a chemotherapeutic agent into a mammal suffering a neoplasm (See lines 1-4 on 7 and claims 1, 3-7, 11-20, 27-31, 33-38 and 41). Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo. Regarding to the limitations of the recitation of "sensitizing" or "preventing" a neoplastic cell to a chemotherapeutic agent, Office considered these recitation as preamble languages, which do not change the manipulating steps of the method comprising administration of reovirus and a chemotherapeutic agent into a population of neoplastic cells that result in a reduction of the neoplastic cells growth in vitro or in vivo. Therefore, the claimed invention is inherently anticipated by the cited reference.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-272-0904. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao Qun Li
May 14, 2004

JAMES HOUSEL 5/17/04
SUPERVISORY PATENT EXAMINER
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